ESC European Society of Cardiology

Europace (2021) **00**, 1–7
https://doi.org/10.1093/europace/euab300

CLINICAL RESEARCH

Theophylline in patients with syncope without prodrome, normal heart, and normal electrocardiogram: a propensity-score matched study verified by implantable cardiac monitor

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Received 17 August 2021; editorial decision 6 November 2021; accepted after revision 16 November 2021

Aims Syncope without prodromes in subjects with normal heart and normal electrocardiogram (ECG) is classified as non-classical neurally mediated syncope and is characterized by low adenosine plasma levels (APLs) and frequent asystolic syncope. We assessed the efficacy of theophylline, a non-selective adenosine receptor antagonist, in preventing syncopal events.

Methods and results Participants received an implantable cardiac monitor, underwent APL measurement, and received oral theophylline at maximum tolerated dose (starting dose 300 mg b.i.d.). They were compared with a historical cohort of untreated patients with implantable cardiac monitor who had the same inclusion criteria and were balanced with the propensity score (PS) method as regard age, sex, lifetime syncopal episodes, APL, and antihypertensive drugs. Primary endpoint was time to first syncopal recurrence at 24 months. There were 76 patients in the theophylline group and 58 in the control group. Syncope recurred in 25 (33%) patients in the theophylline group and in 27 (47%) patients in the control group, with an estimated 2-year recurrence rate of 33% and 60%, respectively, and a hazard ratio of 0.53 [95% confidence interval (CI), 0.30–0.95; $P = 0.034$]. Most of the benefit of theophylline is derived from reduction of syncope due to asystolic atrioventricular (AV) block (hazard ratio of 0.13; 95% CI, 0.03–0.58; $P = 0.008$). Thirty (39%) patients discontinued theophylline after a median of 6.4 (interquartile range 1.7–13.8) months due to side effects.

Conclusion Theophylline was effective in preventing recurrences in patients with syncope without prodromes, normal heart, and normal ECG. The benefit was greater in patients with syncope due to asystolic AV block.

ClinicalTrials.gov Identifier NCT03803215.

Keywords Syncope • Theophylline • Asystole • Implantable loop recorder • Purinergic antagonists • Xanthine

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What's new?

- This was a propensity-score controlled study verified by implantable cardiac monitor aimed to assess the efficacy of theophylline in preventing syncopal recurrences in patients affected by unexplained syncope without prodrome, normal heart, and normal electrocardiogram. Before this study, only few observations were available.
- Theophylline was effective in preventing recurrences with relative and absolute 2-year risk reductions of 45% and 27%, respectively. The number needed to treat was 3.7.
- Most of the benefit of theophylline is derived from reduction of syncope due to asystolic atrioventricular block, with a hazard ratio of 0.13 and a relative risk reduction of 87% in this subgroup.

Introduction

Syncope presenting without (or with very short) prodrome in subjects with normal heart and normal electrocardiogram (ECG) is classified as non-classical neurally mediated syncope.[1] Most patients with such form are characterized by low adenosine plasma levels (APLs).[1,2] In contrast, the most common typical vasovagal syncope is associated with normal-to-high APLs.[3] In patients without (or with very short) prodromes and with normal heart and ECG, the most typical mechanisms of syncope are sudden onset idiopathic paroxysmal atrioventricular (AV) block[4,5] and sinus arrest.[5]

In patients with low APL, asystolic events are explained by the high number of available ligand-free high-affinity A1 receptors, which are much more numerous in the AV node than in the sinoatrial node. In such circumstances, a transient release of endogenous adenosine may be sufficient to block AV and sinoatrial nodal conduction due to the stimulation of a large number of high-affinity A1 receptors. Conversely, if the APL is high and most A1 receptors are saturated, as is the case in patients with typical vasovagal syncope, AV block or sinus bradycardia is less likely to occur.[6–8] Theophylline, a non-selective adenosine receptor antagonist, is potentially able to counteract the effect of adenosine on A1 receptors in patients with low APL. In an intrapatient comparison study,[9] theophylline has proven effective in reducing the burden of syncope and asystole.

In a previous prospective multicentre study,[5] performed in 58 consecutive patients presenting with unexplained syncope, no prodromes, and a normal heart who had received an implantable loop recorder (ILR), we showed that, during a mean observation period of 16 ± 13 months, a diagnosis was established by the ILR in 29 patients (50%); an asystolic pause of 11 ± 5 s due to idiopathic paroxysmal AV block or sinus arrest was present at the time of the diagnostic event in 19 (66%) patients. The population of that study constituted the untreated control group of the present study. In this study, we examined the efficacy of theophylline in preventing syncopal recurrences in a similar population of patients presenting with unexplained syncope, no prodromes, and a normal heart who had received an ILR.

Methods

Theophylline for Unexplained Syncope and low Adenosine (TheoUSA) trial was a multicentre propensity-score controlled study validated by ICM, conducted in 7 Syncope Units in Italy and France between May 2016 and November 2020. The study protocol complied with the provisions of the Declaration of Helsinki and was reviewed and approved by competent ethics committees. Written informed consent was obtained from all participants. The authors had unrestricted access to the data and vouch for the accuracy and completeness of the data and analyses and the fidelity of the trial to the protocol. The study is an investigator-initiated independent clinical study, sponsored by two non-profit scientific organizations: Gruppo Italiano Multidisciplinare per lo Studio della Sincope (GIMSI), Rimini, Italy and Centro Prevenzione Malattie Cardiovascolari N. e V. Corbella, Rapallo, Italy. Data were gathered by the investigators.

The theophylline study group had the same inclusion criteria and study design of the prior study of untreated patients.[5] Both studies prospectively enrolled patients aged 18 years or older, affected by syncope with no or very short (≤5 s) prodromes, normal heart (including normal echocardiogram), and normal ECG, who were referred to ICM implantation for a history of recurrent syncope (at least two episodes during the previous year, or three during the previous 2 years), in agreement with the European guidelines indications. Exclusion criteria were (i) typical vasovagal syncope with long prodromes and situational syncope; (ii) cardiac syncope, orthostatic hypotension, and non-syncopal transient loss of consciousness; (iii) pregnancy or breast-feeding; and (iv) any contraindication to theophylline therapy. Minimal structural or ECG abnormalities, such as mild left ventricular septal hypertrophy in hypertensive patients, mild PR interval prolongation, or history of paroxysmal atrial fibrillation, did not preclude participation in the study.

Following ICM implantation (Biomonitor III, Biotronik, Germany; or Linq, Medtronic, USA), patients were treated with theophylline while waiting for ICM-based diagnosis. Adenosine plasma level was performed in all patients prior to treatment initiation. Slow-release theophylline was started at a dose of 300 mg b.i.d., and then titrated to the maximum tolerated dosage. The initial dosage of 300 mg b.i.d. corresponded to a theophylline plasma level of 11.5 μg/mL, as estimated in a subgroup of 12 patients. Patients were followed-up until the occurrence of the first asystolic syncope or until the end of the study period.

In both study and control groups, baseline APLs were determined by means of high-pressure liquid chromatography, as described elsewhere.[10,11] All APL assays were shipped and analysed in the Laboratory of Biochemistry and Molecular Biology of Timone University Hospital (Marseille, France). Normal laboratory range (5–95% percentile) was 0.40–0.78 μmol/L. Consequently, in this study, low APL was defined as APL <0.40 μmol/L.

Primary endpoint was the time to first syncope recurrence. Secondary endpoint was the time to first asystolic syncope recurrence.

Statistical analysis

Confounding effects between active group and historical control group were minimized by the propensity score (PS) matching and the method of inverse probability of treatment weighting.[12] Specifically, weights were assigned to each patient based on the inverse probability of belonging to the theophylline group. Variables used for PS-weighting included age, sex, lifetime number of syncope events, APL values, and antihypertensive therapy. Assuming 50% syncope recurrence reduction induced by theophylline (from 60% to 30%), 70 patients were needed in the active group to have 90% probability to achieve a two-sided significance level of 0.05 in an exponential model at a log-rank test.

Data were analysed according to the intention-to-treat principle. Continuous data are reported as mean ± standard deviation or median [interquartile range (IQR)] as appropriate. Categorical data are provided as absolute and relative frequencies. The Shapiro–Wilk test was used to check normality of distributions. Continuous variables were compared by non-parametric Mann–Whitney *U*-test and proportions by the Fisher's exact test.

The incidence of study endpoint events was estimated by the product-limit method, and Kaplan–Meier plots were generated. Hazard ratios (HRs) and 95% confidence intervals (CIs) of study endpoint events in the theophylline vs. control group were estimated with multivariable PS-weighted proportional-hazard Cox regression models, using variables with >0.1 residual standardized difference after PS-weighting as covariates. The analysis was performed with the R Studio software version 4.0.3. Statistical significance was set at $P < 0.05$ in all tests.

Results

Population

The theophylline group included 76 patients (mean age 60 years, 62% female). The initial dosage had to be reduced in 32 (42%) patients due to side effects. After titration, the mean dose was 383 ± 333 mg per day. The characteristics of theophylline patients and controls are compared in *Table 1*. The study groups were well matched for age, sex, adenosine value, history of syncope, and antihypertensive therapy. Low APLs were observed in 49 (64%) of theophylline patients and 45 (78%) of controls [median APL 0.2 µmol/L (IQR 0.1–0.3) and 0.15 µmol/L (IQR 0.1–0.25), $P = 0.98$].

Outcome

During a mean follow-up of 15 ± 11 and 16 ± 13 months, in the intention-to-treat analysis, syncope recurred in 25 patients in the theophylline group (33%) and 27 patients in the control group (47%), *Table 2*. The respective product-limit estimate of 2-year syncope recurrence rate was 33% in the theophylline group and 60% in the control group (adjusted PS-weighted HR, 0.53; 95% CI, 0.30–0.95; $P = 0.034$). The Kaplan–Meier plot is shown in *Figure 1*. Three patients in the theophylline group had syncope recurrence after discontinuation of theophylline due to treatment-related side effects.

Asystolic syncope occurred in 13 patients in the theophylline group (17%) and 17 patients in the control group (29%). The mean length of asystolic pauses was 11.5 ± 6.5 s and 10.6 ± 5.1 s, respectively. The product-limit estimate of 2-year asystolic syncope recurrence rate was 22% in the theophylline group vs. 47% in the control group (adjusted PS-weighted HR, 0.36; 95% CI, 0.16–0.80; $P = 0.013$). *Figure 2* displays relative Kaplan–Meier plots.

In an exploratory analysis, significantly fewer patients had syncope due to AV block in the theophylline group than in control group, 2 (3%) vs. 7 (12%), adjusted PS-weighted HR, 0.13; 95% CI, 0.03–0.58; $P = 0.008$. There was a trend for lower rate of syncope due to sinus

Table 1 Characteristics of the study groups

Variables	Theophylline patients ($n = 76$)	Control patients ($n = 58$)	*P*-value
Age, years	60 ± 16	63 ± 14	0.14
Females	44 (58)	36 (62)	0.72
Low adenosine	49 (64)	45 (78)	0.13
Plasma adenosine level (µmol/L)	0.20 (0.10–0.30)	0.15 (0.10–0.25)	0.98
History of syncope			
No prodromes	39 (51)	34 (59)	0.48
Occasional short prodromes	27 (49)	24 (41)	0.59
Lifetime number of syncopes	4.5 (3–8)	4 (3–7)	0.27
Syncope episodes/previous 2 years	3 (2–4.5)	3 (2–4)	0.40
Duration of syncope history, years	4 (1–8)	2.5 (1–5)	0.21
Age of first syncope, years	54 (37–70)	62 (45–71)	0.06
Syncope-related mild injuries	45 (62)	27 (47)	0.16
Syncope-related major injuries	23 (32)	19 (33)	0.85
Minimal ECG or cardiac abnormalities	8 (11)	3 (5)	0.39
Antihypertensive therapy	28 (38)	25 (43)	0.48
ACE/ARB	23 (30)	18 (31)	1.00
Diuretics	7 (10)	4 (7)	0.76
Ca-antagonists	6 (8)	7 (12)	0.56
Beta-blockers	11 (15)	4 (7)	0.27
Alpha antagonists	1 (1)	0 0	1.00
Tilt table test			
Performed	75 (99)	53 (91)	0.08
Positive	34 (45)	24 (45)	0.73
Positive with asystolic pause >3 s	5 (15)	5 (9)	0.75

ACE, angiotensin-converting enzyme; ARB, angiotensin-receptor blocking; ECG, electrocardiogram.

Table 2 Primary and secondary clinical endpoints

	Theophylline ($n = 76$)	Controls ($n = 58$)	Adjusted PS-weighted Hazard ratio (95% CI)	*P*-value
Primary endpoint: syncope recurrence, *n* (%)	25 (33)	27 (47)	0.53 (0.30–0.95)	0.034
Secondary endpoint: asystolic syncope recurrence, *n* (%)	13 (17)	17 (29)	0.36 (0.16–0.80)	0.013
Sinus arrest	11 (14)	10 (17)	0.44 (0.18–1.05)	0.07
AV block	2 (3)	7 (12)	0.13 (0.03–0.58)	0.008

AV, atrioventricular; CI, confidence interval; PS, propensity score.

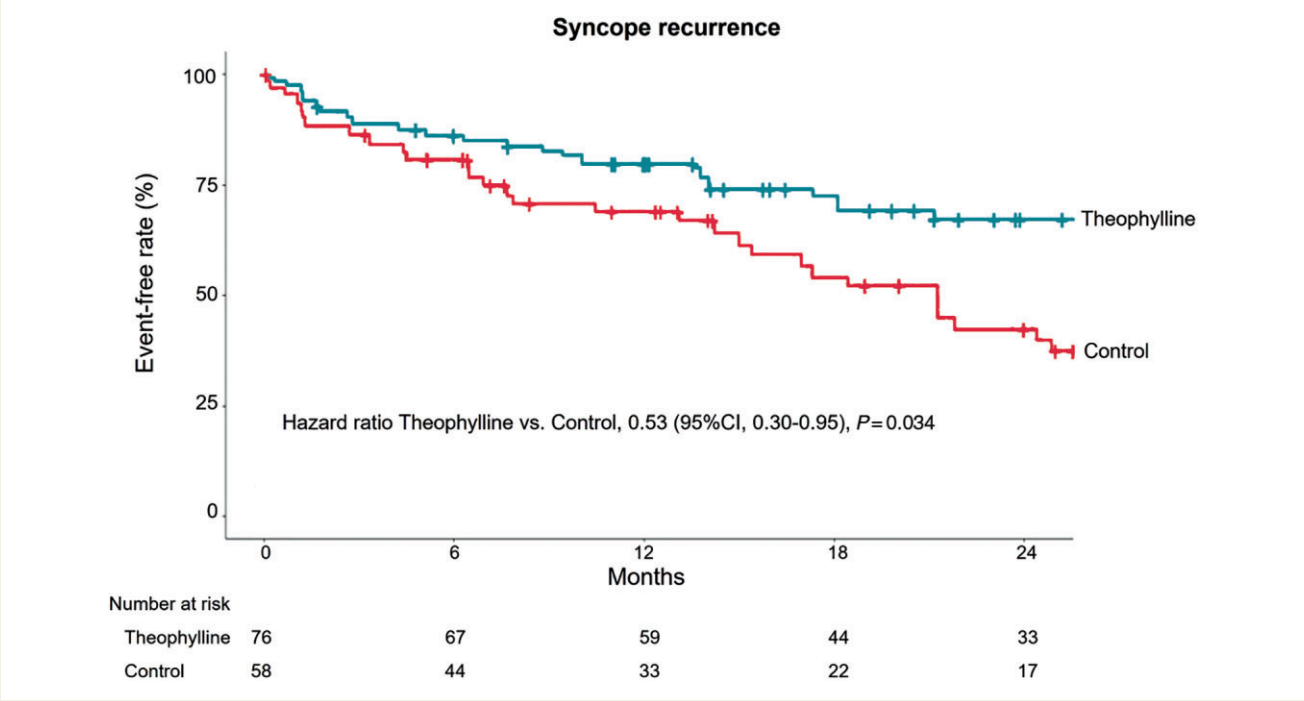

Figure 1 Kaplan–Meier plots of syncope-free rate in theophylline and control groups. The respective product-limit estimate of 2-year syncope recurrence rate was 33% in the theophylline group and 60% in the control group. CI, confidence interval.

arrest in theophylline group than in the control group, 11 (14%) vs. 10 (17%), adjusted PS-weighted HR, 0.44; CI, 0.18–1.05; $P = 0.07$ (*Figure 3*).

A subgroup analysis of low vs. normal/high APL was performed in the theophylline group. Results indicated no difference in treatment effect between these two subgroups for both primary endpoint events (PS-weighted HR, 0.98; 95% CI, 0.42–2.27; $P = 0.96$) and secondary endpoint events (PS-weighted HR, 0.96; 95% CI, 0.30–3.13; $P = 0.96$).

The study was hampered by discontinuation of theophylline therapy in 30 (39%) patients before syncope recurrence after a median of 6.4 (IQR 1.7–13.8) months, due to intolerable side effects. The following side effects were reported: gastrointestinal complaints in 17 cases (nausea, vomiting, loss of appetite, dry mouth, diarrhoea, and abdominal pain); neurological symptoms in 10 cases (tremors, insomnia, and headache); and cardiovascular symptoms in 7 cases (tachycardia, palpitations, and hypertension). No severe treatment-related adverse events occurred.

Other clinical events

Non-syncopal asystolic pauses >3 s were recorded in four patients in the theophylline group and in two controls. These events were not included in the analysis by protocol definition. In the theophylline group, three patients had multiple asystolic events documented by ICM soon after the first syncopal event. Seven patients received pacemaker implantation after documented asystolic syncope. Two patients had paroxysmal atrial fibrillation and two had paroxysmal supraventricular tachycardia. One patient died from acute myocardial infarction.

Discussion

In this study, theophylline was effective in preventing recurrences in patients with syncope without prodromes, normal heart, and normal ECG. The relative and absolute 2-year risk reductions were 45% and 27%, respectively. The number needed to treat was 3.7. Most of the

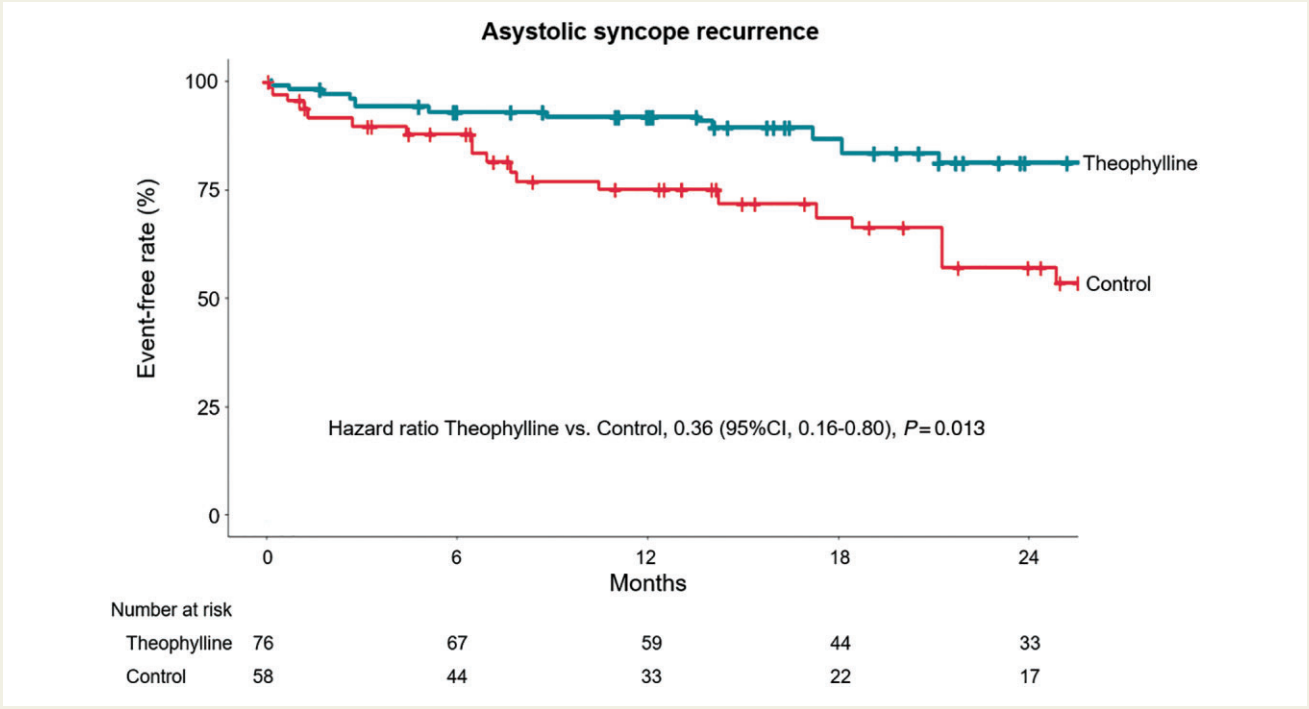

Figure 2 Kaplan–Meier plots of asystolic syncope-free rate in Theophylline group and in Control group. The respective product-limit estimate of 2-year syncope recurrence rate was 22% in the theophylline group vs. 47% in the control group. CI, confidence interval.

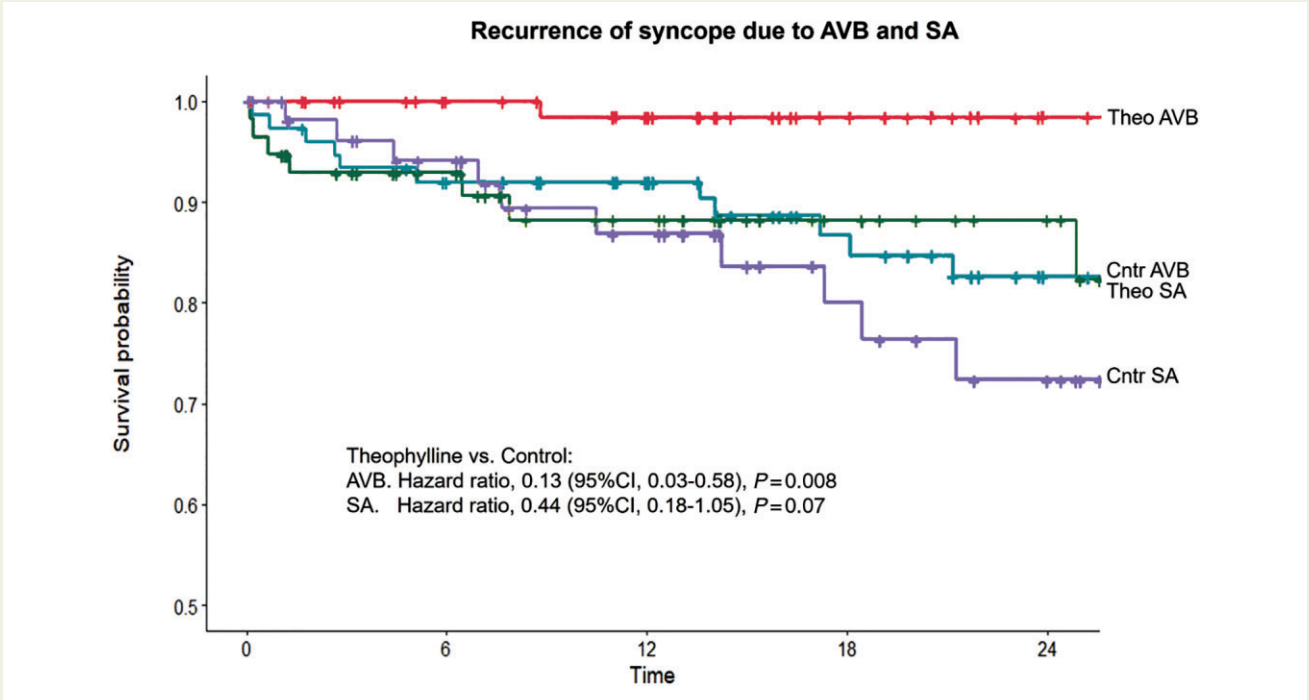

Figure 3 Kaplan–Meier plots of syncope due to AVB and to SA in Theophylline group and in Control group. AVB, atrioventricular block; SA, sinus arrest.

benefit of theophylline is derived from reduction of syncope due to asystolic AV block, with a hazard ratio of 0.13 and a relative risk reduction of 87% in this subgroup. This finding supports the hypothesis that the activation of A1 receptors, which are mostly located in the AV node and, with less extent, in the sinoatrial node, plays a role in causing prolonged asystole and syncope in predisposed patients and that theophylline-induced blockade of such receptors prevents their activation.

A previous study from our group[9] described the results of an intra-individual comparison in 16 patients with low APL and previously documented asystolic syncope, showing that theophylline was highly effective in reducing syncope burden (from 2.6 to 0.4 per year) and asystole burden (from 9.6 to 1.1 per year) vs. no treatment. Notably, both studies showed evidence of greater benefit in patients in which the mechanism of syncope was an asystolic AV block. In the previous study,[9] syncope recurred at 2 years in 0% of patients who had an idiopathic AV block as the index event and in 58% of patients who had syncope due to sinus arrest, $P = 0.005$ at Kaplan–Meier product-limit estimate. The results of the present study are consistent showing that only 3% of patients had recurrence of syncope due to asystolic AV block.

The efficacy of theophylline depends on the relative contribution to syncope of the adenosine pathway as compared to the sympathovagal pathway. The former is supposed to be more relevant to patients with no prodromes and normal heart and ECG, while the latter is more relevant to patients with typical vasovagal syncope. This physiopathological difference provides an explanation for the variable efficacy of theophylline therapy as reported in the literature in the absence of APL assay.[13–16] Since theophylline competes with adenosine for receptor binding, drug treatment is expected to be more effective when APLs are low and most A1 receptors are free, as theophylline can prevent receptor activation in case of APL increase. In patients with typical vasovagal syncope, the adenosine pathway has a more limited role in triggering syncope since chronic exposure to high APL likely determines a down-regulation of adenosine receptors. Moreover, high APL leads to A1 receptor saturation, thus preventing theophylline from receptor binding and limiting its potential therapeutic effects.[17,18] However, we may suppose that these two situations coexist in many patients, thus determining the overlap of different forms of reflex syncope that is commonly observed in clinical practice.

In this study, the effect of theophylline was consistent in both low and normal/high APL subgroups. This finding was unexpected because low APL is a landmark of patients affected by syncope without prodromes, normal heart, and normal ECG.[2,5] Owing to the relatively small numbers of patients with normal APL, a type II error cannot be excluded. However, the findings of this study are unable to show a causal relationship between APL and effect of theophylline, as the receptor antagonist of adenosine. Although adenosine binding is expected to be prevalent in high-APL patients, we cannot exclude that theophylline may exert some antagonist effects through low-affinity A2 receptors located in the vascular smooth muscles and thus prevent vasodilation in high-APL patients.[19] Moreover, theophylline might have other pharmacological effects, particularly its effect via cyclic AMP causing an essentially a sympathomimetic action. As a result of a subgroup analysis, this hypothesis must be confirmed in future studies, which should also investigate the role of APL in the selection of treatment candidates. However, it may contribute to explaining the variability of theophylline efficacy.

The results of this study were hampered by dose reduction or discontinuation of theophylline therapy in many patients, due to intolerable side effects. The discontinuation rate was higher than that reported in our previous study,[9] in which only two (12%) patients discontinued treatment with theophylline. There are several possible explanations for this contrasting finding. First, it should be considered that, in the previous study,[9] patients started theophylline after documentation of asystolic episodes and were therefore aware that they were receiving a disease-specific therapy. Conversely, in this study, patients accepted theophylline as preventive therapy, i.e. before an established diagnosis. This may have significantly hampered patients' compliance and motivation. Second, the maximum tolerated dose achieved after dose titration was lower on average in the present than in the previous study (383 vs. 520 mg per day). The lower dose was probably a consequence of reduced compliance. Third, clinical characteristics of populations were different, as participants were older (61 vs. 47 years) and reported a lower number of syncopal episodes (5 vs. 8 episodes) in the present than in the previous study. Of note, although reported side effects had a considerable impact on patients' compliance, no severe treatment-related events were reported. Theophylline can thus be considered a safe treatment option in these patients.

Limitations

We did not carry out a strict monitoring of participants' adherence to treatment through pill count. As study compliance was low, it is likely that some patients missed a regular daily consumption, thus increasing the failure rate of the therapy. Actually, three patients had syncope recurrence after theophylline discontinuation, thus decreasing the per-treatment recurrence rate to 29%.

COVID-19 pandemic had a substantial impact on the running of the trial. At the outbreak of the COVID-19 pandemic in February 2020, patient recruitment and follow-up were still ongoing and were significantly affected by the pandemic status, despite a mitigation plan that was instituted including remote monitoring to avoid patients access to the clinic. We are unable to predict what influence COVID-19 might have had on treatment effects, but it is plausible that lower recruitment and a general lack of protocol compliance could have led to underestimated treatment effect.

Conclusion and perspectives

The results of this study provide further evidence that some patients with syncope without prodrome, with normal heart and normal ECG, may benefit from theophylline therapy. Theophylline can represent a safe treatment option in these patients, although a chronic treatment should be discouraged in patients with side effects. Since the effect of theophylline is mostly derived from reduction of syncope due to asystolic AV block, monitoring patients by ECG tracing and starting theophylline therapy only in those exhibiting AV block at syncopal relapse, may be a valid alternative strategy.

Our study provides the rational to further investigate the efficacy of adenosine antagonists in larger randomized parallel trials, which

should preferably also include molecules with more favourable risk-benefit profile.

Acknowledgements

The authors would like to thank Daniele Giacopelli and Alessio Gargaro (Research Clinical Unit, Biotronik Italy, Vimodrone, Italy) for statistical analysis, and Dejan Danilovic for critical text review and editing.

Funding

The study was an investigator-initiated independent clinical study, supported by two non-profit scientific organizations: Gruppo Italiano Multidisciplinare per lo Studio della Sincope (GIMSI), Rimini, Italy and Centro Prevenzione Malattie Cardiovascolari N. e V. Corbella, Rapallo, Italy. Data were gathered by the investigators.

Conflict of interest: P.N. is an employee of Biotronik Italia, an affiliate of Biotronik SE & Co. KG. The other authors have no conflict of interest to declare.

Data availability

The data will be available upon reasonable request to the corresponding author.

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